DRUG DESIGN

edited by E. J. Ariëns

Volume IV

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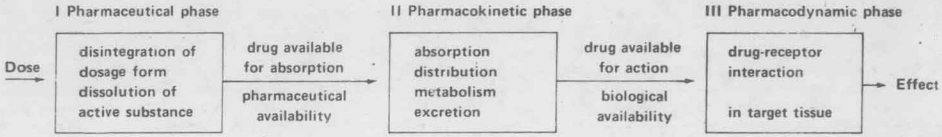
Preface



In drug action three main phases can be distinguished. In the first phase, the pharmaceutical one, the quantity of drug available for absorption is determined. In this phase the disintegration of the dosage form—tablet, capsule, etc.—and the dissolution of the active compound take place. The fraction of the dose that becomes available in a form suitable for absorption can be indicated as the pharmaceutical availability of the active compound in the drug preparation.

The pharmacokinetic phase, comprising absorption, distribution, excretion, and metabolic conversion of the drug, follows. In this phase the concentration of the active compound in the plasma and thus in the target tissues and at the sites of action—the specific receptors—is determined. The fraction of the dose that reaches the circulation after absorption is known as the biological availability. The losses due to the initial passage through the liver in cases of oral application are taken into account.

The pharmacodynamic phase comprises the interaction between the drug and its molecular sites of action—the specific receptors—which leads to the induction of a stimulus and generation of the effect.

In addition to the relation of pharmaceutical and biological availabilities to therapeutic efficacy, the relation between time and plasma concentration, representing the bioavailability profile, is of importance.

In Volumes I, II, and III of this treatise attention was focused chiefly on the aspects of the pharmacokinetic and pharmacodynamic phases of drug action of importance to drug design. The major part of this volume is devoted to the

pharmaceutical phase of drug action, with emphasis on those aspects that are of importance in the design of optimally effective drug products. Additional chapters on this aspect of drug design will appear in Volume V, including one outlining the approaches used in the formulation of agricultural pesticide products demonstrating, among other things, similarities to those followed in the design of optimal drug products.

In an effort to illustrate the parallelism which exists in the approaches to drug design, many different types of pharmaceuticals—such as those used for their therapeutic action, as well as those used as insecticides, weed killers, food additives, and insect sterilants—are discussed in this treatise. Hopefully, this will promote fruitful communication among investigators in these related disciplines.

E. J. ARIËNS

Contents of Other Volumes

VOLUME I

VOLUME II

VOLUME III

Contents

Chapter 1 Biopharmaceutics as a Basis for the Design of Drug Products

Leslie Z. Benet

I. Introduction

In 1971 biopharmaceutics, the word, the term, the field, the science, entered into its second decade. The word originated as a result of a search for a title to describe a new pharmacy course. At the University of California School of Pharmacy, in the mid-1950's a new pharmacy course was developed around material which covered the physiological and dosage form factors affecting the release of drugs from manufactured dosage forms, or in more general terms from drug delivery systems. In 1960, Dr. Gerhard Levy suggested the

word "biopharmaceutics," and in the subsequent year this term became the official title for the course. In the same year, Dr. John G. Wagner published the first review of a great deal of studies dealing with the absorption aspects of drug delivery systems, then compiled under the new term, biopharmaceutics (*1*). The growth of the field during the last decade and the interest generated in its application is reflected in the number of broad surveys of the field which have been published at the close of this first ten-year period. Gibaldi (*2*) and Levy (*3*) have prepared excellently documented broad introductory overviews of the principles and concepts of biopharmaceutics. Wagner has written an encyclopedic text (*4*) while Swarbrick has compiled a series of reviews of specific areas within the field (*5*). Readers of the present series are well aware of the excellent chapters prepared by Wagner and van Rossum in *Drug Design*, Volume I (*6*). In addition to these descriptive presentations and other texts (*7*, *8*), the APhA Academy of Pharmaceutical Sciences prepared a most useful "Guidelines for Biopharmaceutical Studies in Man" in response to a need for a critical analysis and evaluation of current concepts related to this area of drug product evaluation (*9*).

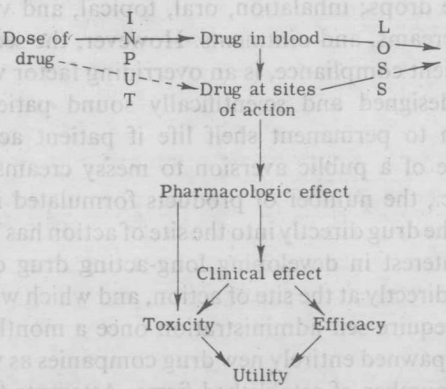
With the wealth of good material already available, it would be superfluous to present another general overview of the area. Instead, this chapter will attempt to present a number of general principles within a conceptual framework which hopefully will serve as a strategy in the design of the appropriate drug delivery system for a new therapeutic candidate. In most cases extended discussions will be limited to newer concepts and more recent references. However, references to the classical studies in biopharmaceutics will also be included, so that the reader may gain an historical perspective of a particular dosage design strategy by reading the original work or by consulting one of the previously mentioned overviews (*2–6*).

Wagner (*6*) has defined biopharmaceutics as "the study of the relationships among: (1) the physical and chemical properties of the drug, (2) the physicochemical and pharmaceutical properties of the dosage form, (3) physiological factors, (4) pharmacokinetic parameters, and (5) biological, pharmacological, and clinical effects." Gibaldi (*2*) has succinctly described it as "the branch of pharmaceutical science concerned with the relationship between physicochemical properties of a drug in a dosage form and the therapeutic response observed after its administration." The Guidelines (*9*) define biopharmaceutics as a "study of the factors influencing the bioavailability of a drug in man and animals and the use of this information to optimize pharmacologic or therapeutic activity of drug products in clinical applications." This last definition seems more appropriate for a chapter about drug dosage form design and is similar to the operational definition presented here. Biopharmaceutics is the study of all the controllable variables which the investigator can manipulate (or avoid) in order to "input" a drug to its site of action.

II. Biopharmaceutics—The Science of Input

In a recent article (*10*) the author proposed a simplified mathematical approach for deriving pharmacokinetic models, in which he presented a method whereby the equation describing the time course of a drug in the blood or plasma can be determined from the product of an input function and a disposition function. Disposition functions describe everything that happens to a drug (i.e., distribution, metabolism, and unidirectional elimination by all routes) after it gets into the blood circulation, or more correctly, after it is administered by intravenous (IV) injection into a peripheral vein. Input functions describe the processes necessary to get the drug into the bloodstream. For most drugs disposition is independent of input, and therefore the changes we see in efficacy from product to product, route of administration to route of administration, and dose to dose are directly related to the input process of the active chemical entity. Biopharmaceutics is the study of these input processes.

When any member of the health team administers a dose of a drug, his ultimate interest in that drug relates to the utility of the drug in the patient. This is illustrated in Scheme 1. In most cases a dose of a drug is input into the biological system in such a way as to give sufficiently high blood levels so that an adequate quantity of the drug will reach the site of action. Simultaneously, there will be loss of drug from the system by the disposition processes. As a result of sufficiently high drug concentrations at various sites in the body, a number of measurable pharmacologic effects will be elicited, some of which may be the desired clinical effect. However, a number of the pharmacologic



Scheme 1. A schematic representation of the dose–efficacy relationship for a drug.

effects and even a hyperactive clinical effect, may result in toxic manifestations. The utility of any dose of a drug thus must be measured by weighing the efficacy achieved from the clinical effect against the toxicities observed. However, the model illustrates a very attractive alternative to drug dosing. If the clinician could input the drug directly into the site of action, he would need a lower dose to achieve the clinical effect, and would consequently keep drug concentrations to a minimum at other toxic sites of action. In addition, he should achieve clinical efficacy in a much shorter period of time. This leads to the first principle in our strategy for drug product design.

Principle 1: *The dosage form should allow the drug to reach the site of action as quickly and completely as possible, without undue inconvenience to the patient.*

Unfortunately, when a single sentence is used to express an idea, a number of words in that sentence can be interpreted in many ways. The author must immediately reject certain interpretations of those words. Thus some principles in this chapter will be followed by an appropriate disclaimer.

Disclaimer for Principle 1: "Quickly" and "completely" should not be interpreted as meaning that all dosage forms should instantaneously release the entire dose at the site of action. In many cases, this would lead to the toxicity that results from a hyperactive clinical effect. Most drugs, however, are designed to give a continuing effect either because the drug molecule was designed to have disposition properties that maintain its concentration at the site of action, or because the dosage form was designed to release the drug slowly (see Chapters 2 and 3 of this volume). Therefore, "quickly" means that when a drug is supposed to go to its site of action, it gets there rapidly; "completely" means that all the drug in the product reaches its site of action.

The first half of the principle has served as the rationale for the development of eye, ear, and nose drops; inhalation, oral, topical, and vaginal aerosols; and topical lotions, creams, and ointments. However, the second part of the principle, willing patient compliance, is an overriding factor which will doom the most logically designed and scientifically sound patient-administered drug delivery system to permanent shelf life if patient acceptance is not forthcoming. Because of a public aversion to messy creams, drippy drops, greasy ointments, etc., the number of products formulated in drug delivery systems which input the drug directly into the site of action has been decreasing. However, recently interest in developing long-acting drug delivery systems which may be placed directly at the site of action, and which will be convenient since they will only require self-administration once a month, or at possibly longer intervals, has spawned entirely new drug companies as well as new drug delivery groups in a number of established firms. Attempts to develop small plastic disks for placement in the eye (similar to a contact lens) which will

slowly release drug into the humoral fluid, and drug-impregnated plastic rings or loops which when placed in the uterus will release controlled amounts of contraceptive agents, are drug product designs consistent with Principle 1.

Figure 1 depicts the various routes by which a drug may be "inputed" into the body and will serve as a model for examining the bioavailability of a drug. Bioavailability has a specific definition with respect to a drug reaching the

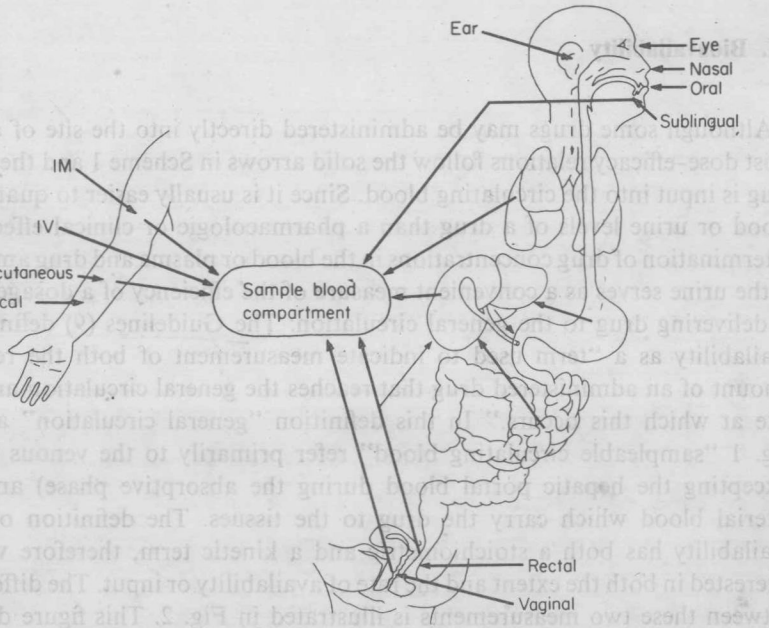


Fig. 1. The various routes and pathways by which a drug may be "inputed" into the body. The diagram is especially useful in explaining the first pass effect following oral dosing where drug absorbed from the small intestine or stomach must pass through the liver and therefore be subject to metabolism or biliary excretion before reaching the sampleable blood.

blood circulation, as will be discussed subsequently. However, Principle 1 alludes to the rate ("quickly") and extent ("completely") of availability with respect to drug reaching the site of action. It is ironic that drug delivery systems which are designed in accordance with Principle 1 may not be feasibly marketed since the manufacturer may not be able to devise a control procedure which can measure the drug's bioavailability at the site of action. For example, the extent and rate of availability for an orally administered drug can be assessed by measuring blood levels, whereas for a drug "inputed" into a site of action, significant blood levels would indicate distribution away from the site of